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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 12/10/10 has been entered.

Status of Application, Amendments and/or Claims

The amendment of 12/10/10 has been entered in full. Claims 11, 16 and 22 are amended. Claim 15 and 23 are canceled (claims 14 and 17 were previously canceled).

Claims 1-13, 16, and 18-22 are pending in the instant application.

Claims 1-10 and 18-21 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicants timely traversed the restriction (election) requirement in the reply filed on 6/8/09.

Claims 11-13, 16 and 22 are under consideration, in so far as they are drawn to the elected species.

Information Disclosure Statement

The Information Disclosure Statement of 3/10/11 has been considered.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (4/13/10).

All rejections of claims 15 and 23 are moot in view of Applicants' cancellation of these claims.

The objections to claim 11 at pg 3 and 9, and to claim 22 at pg 9 are *withdrawn* in view of Applicants' amendments to the claims.

The rejections of claims 11-13, 16 and 22 under 35 U.S.C. § 112, first paragraph at pg 3-7 for failing to provide enablement for the full scope of the claims, and at pg 7-8 for failing to comply with the written description requirement, are *withdrawn* in view of (1) Applicants' amendments to the claims, and (2) Applicants' persuasive arguments at pg 9-11 of the 12/10/10 response. Specifically, it is found persuasive that the specification provides enablement and written description for the claimed method with respect to the scope of CNP or derivative thereof now recited in amended claims 11 and 22 (and claims dependent therefrom). The Examiner notes that the term "CNP activity" as now recited in claims 11 and 22 is defined in the specification as referring to "the activity to act on GC-B to increase guanyl cyclase activity or the activity to significantly increase the body height of an individual" (¶ 68 of the published application).

The objection to the specification at pg 8-9 is *withdrawn* in view of Applicants' amendments to page 12 of the specification.

The rejection of claims 11-13, 16 and 22 under 35 U.S.C § 112, second paragraph, at pg 9-10 for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is *withdrawn* in view of Applicants' amendments to the claims.

The rejection of claims 11-13, 16 and 22 under 35 U.S.C. § 112, first paragraph at pg 10-12 for failing to comply with the written description requirement because the claim contain new matter is *withdrawn* in view of Applicants' amendments to the claims.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the

various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicants are advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11-13, 16 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miyazawa et al (2002. Endocrinology. 143(9): 3604-3610; cited previously), and further in view of Suda et al, 1998 (Proc Natl Acad Sci USA; reference CA on the 11/25/09 IDS). This rejection was set forth previously at pg 12-16 of the 4/13/10 Office Action.

In the rejection set forth in the 4/13/10 Office Action, the fourth sentence on page 14 inadvertently included the word "systemically", which lead to this sentence indicating that Miyazawa taught systemic administration, whereas the next sentence then indicated that Miyazawa did not teach systemic administration. The rejection set forth previously is restated herein (1) to clarify for the record that Miyazawa et al do not teach systemic administration; (2) to clarify the reasoning for the obviousness of combining the references; and (3) in view of Applicants' amendments to the claims.

The recitation of "for increasing the body height of an individual free from FGFR3 abnormality" in the preamble of claim 11 is interpreted as an intended use and bears no accorded patentable weight to distinguish the claimed method over one from the prior art, except in so far as it limits the method to a particular patient population (an individual free from FGR3 abnormality). Likewise, the recitation that the administration is "to increase the body height in the individual" is interpreted as an intended use because it simply states what the administration is to be used for. The instant specification defines a "FGFR3 abnormality" as referring to achondrogenesis or achondroplasia caused by growth inhibition of cartilage bones resulting from mutations in the FGRF3 gene; thus an "individual free from FGRF3 abnormality" includes any individual without a mutation in FGRF3. Therefore, claim 11 encompasses a method comprising administering systemically C-type natriuretic peptide (CNP) in an individual without a

FGRF3 mutation and with growth cartilage layers, wherein the CNP is CNP-22 of SEQ ID NO: 1. In the Sequence Listing, SEQ ID NO: 1 is indicated to be the sequence of human CNP-22; however, mouse CNP-22 has an identical amino acid sequence (see pg 331 of Komatsu et al, 2002. J Bone Miner Metab. 20: 331-336; cited previously; cited here solely to provide evidence of inherency).

Miyazawa et al teach a transgenic mouse that overexpresses CNP in a wildtype background (pg 3605). Miyazawa et al teach that the CNP transgenic mice exhibit elongated limbs similar to BNP transgenic mice, and cite Suda et al as a reference for BNP transgenic mice (pg 3605). The mice were generated by "targeted expression of CNP in the growth plate chondrocytes under control of the mouse pro-α1 (II) collagen (Col2a1) promoter" (pg 3605). These mice do not have a mutation in the FGFR3 gene and have growth cartilage layers. Furthermore, the CNP gene used in these mice was the mouse CNP gene; therefore they produced mouse CNP-22. See page 3605 of Miyazawa et al, which refers to reference 17 for construction of the transgenic mice. Reference 17 is Chusho et al, 2001 (PNAS. 98(7): 4016-4021; reference CB on the 9/29/06 IDS), which teaches on page 4016 that the mouse CNP gene is used in the transgenic mice (Chusho is cited here solely to provide evidence that the mice used by Miyazawa express the mouse CNP-gene). As described above, mouse CNP-22 produced by the mouse CNP gene is 100% identical to SEQ ID NO: 1. Therefore, Miyazawa et al teach a method comprising administering C-type natriuretic peptide (CNP) in an individual without a FGRF3 mutation and with growth cartilage layers, wherein the CNP is CNP-22 of SEQ ID NO: 1.

Miyazawa et al do not teach systemic administration of CNP-22 of SEQ ID NO: 1.

Suda et al teach generation of BNP-transgenic mice under the control of the human serum amyloid P component promoter (pg 2337). Suda et al further teach "We report here marked skeletal overgrowth in transgenic mice that overexpress BNP. Transgenic mice with elevated plasma BNP concentrations exhibited deformed bony skeletons characterized by kyphosis, elongated limbs and paws, and crooked tails" (see Abstract). Suda et al further teach "In the present study, we also observed that CNP, a selective activator of GC-B, increases the total longitudinal bone growth and cGMP

production in cultured embryonic mouse tibias more potently than BNP, an activator of GC-A. These findings suggest strongly that activation of chondrogenesis by natriuretic peptides is mediate primarily by GC-B. Because BNP is overproduced specifically by the liver and not in the bone from BNP-transgenic mice, we postulate that BNP secreted into the circulation in a large quantity cross-reacts with GC-B in the growth plate chondrocytes, thereby causing skeletal overgrowth of vertebrae and long bones in these animals ... It is tempting, therefore, to speculate that CNP is the endogenous ligand for GC-B in the bone in vivo and is involved in the process of endochondral ossification" (pg 2341).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute the human serum amyloid-P component promoter used by Suda et al for the mouse pro-α1 (II) collagen (Col2a1) promoter in the CNP-transgenic mice taught by Miyazawa, thus creating a CNP-transgenic mice wherein CNP-22 of SEQ ID NO: 1 is expressed systemically in the plasma rather than locally in collagen. By creating such a mouse, the skilled artisan would practice a method encompassed by claim 11, comprising administering systemically a CNP-22 of SEQ ID NO: 1 to an individual free of FGRF3 abnormality and having growth cartilage layers. The person of ordinary skill in the art would have reasonably predicted that systemic expression of CNP-22 in the plasma would result in increased bone growth in the same manner as systemic expression of BNP in the plasma. This result was predictable because Suda et al teach that CNP promotes greater growth *in vitro* than BNP, suggesting that CNP is the actual ligand for GC-B in the bone, and because Miyazawa demonstrates that CNP transgenic mice have the same elongated limb phenotype as BNP transgenic mice. Thus, creating a transgenic mouse according to Miyazawa et al except for substituting the systemic promoter of Suda et al for the local promoter of Miyazawa et al represents combining prior art elements according to known methods to yield predictable results, in accord with *KSR Int'l Co. v. Teleflex Inc., 550 U.S 398 (2007 (KSR).* The skilled artisan would have further had a reasonable expectation of success in creating said transgenic mice because it would have simply required creating CNP transgenic mice as previously described, but with a simple substitution of one promoter

known in the art for local expression for another known in the art for systemic expression. The skilled artisan would have had a reasonable expectation of success in expressing CNP systemically because of the success of Suda et al in expressing BNP systemically.

Claims 12 and 13 each encompass a method of claim 11 wherein the increase in body height is due to an extension of cartilage bones that are tibiae. Thus, each dependent claim solely limits the intended use of claim 11, and is therefore unpatentable over Miyazawa et al in view of Suda et al for the same reasons as for claim 11 described above.

As amended, claim 16 depends from claim 11 and recites that the CNP is the CNP-22 of SEQ ID NO: 1 or CNP-53 of SEQ ID NO: 2. The rejection set forth above was directed to the embodiment wherein the CNP is the CNP-22 of SEQ ID NO: 1. Therefore, claim 16 is unpatentable over Miyazawa et al in view of Suda et al for the same reasons as for claim 11 described above.

Claim 22 is an independent claim that differs only from claim 1 in the intended uses recited in the claim. The recitation of "for extending a cartilage bone free from FGFR3 abnormality in an individual" in the preamble of claim 22 is interpreted as an intended use and bears no accorded patentable weight to distinguish the claimed method over one from the prior art, except in so far as it limits the method to a particular patient population (an individual free from FGR3 abnormality). Likewise, the recitation that the administration is "to activate guanyl cyclase B (GC-B) in the individual" is interpreted as an intended use because it simply states what the administration is to be used for. Therefore, claim 22 encompasses a method comprising administering systemically C-type natriuretic peptide (CNP) in an individual free from FGRF3 mutation and with growth cartilage layers, wherein the CNP is CNP-22 of SEQ ID NO: 1. Therefore, claim 22 is unpatentable over Miyazawa et al in view of Suda et al for the same reasons as for claim 11 described above.

Applicants' arguments (10/12/10; pg 13-14) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that the statement in the rejection that Miyazawa et al teach systemic administration is not correct. Applicants argue that the "CNP expression in the Tg mouse as described by Miyazawa, was confirmed only in chondrocytes" and is "different from systemic administration" (pg 13).

This argument has been fully considered and is found to be persuasive, but the rejection is maintained for the reasons set forth above. As described above, the fourth sentence on page 14 of the previous Office Action inadvertently included the word "systemically", which lead to this sentence indicating that Miyazawa taught systemic administration, whereas the next sentence indicated that Miyazawa did not teach systemic administration. The restated rejection set forth above clarifies for the record that Miyazawa et al do not teach systemic administration. The combination of the teachings of the references of Miyazawa et al and Suda et al renders the systemic administration obvious for the reasons set forth above.

Applicants point to *International v. Teleflex Inc* (2007) as stating that the operative question regarding obviousness of a combination of known elements is "whether the improvement is more than the predictable use of prior art elements according to their established function". Applicants further argue that the rejection speculates "a relationship between CNP and GC-B, and does not provide a motivation for systemically administering CNP". Applicants argue that it was known at the time of filing of the instant application that "CNP is a molecule different from ANP or BNP". Applicants argue that "BNP is mainly produced in the heart and serves as a hormone peptide secreted into blood plasma from heart" whereas CNP "is exclusively produced in the brain" (pg 14). Applicants submit the references of Tawarangi et al (1991) and Kojima et al (1990) in support of this argument. In view of this, Applicants argue that the ordinary artisan at the time the invention was made could not have reasonably predicted (1) "whether or not CNP exhibits similar effects both in vivo or in vitro", (2) "the effects which are obtained when the concentration of CNP in blood plasma is elevated by systemic administration, rather than local administration", or, consequently, (3) "the advantages of the claimed invention from the combination of Miyazawa and Suda" (pg

14). Applicants further argue that "Suda does not provide any motivation to systemically administering CNP" (pg 14).

These arguments have been fully considered but are not found persuasive. The references of Tawarangi et al and Kojima et al have been fully considered. It is acknowledged that Tawarangi et al (1991) and Kojima et al (1990) teach that CNP is expressed exclusively in the brain. However, subsequent to these publications in the early 1990's, the relevant art showed that CNP was y shown to be expressed in a variety of tissues. As evidence of this, Kiemer et al (2002) teach that "CNP is suggested to be the major NP in the brain, but its expression was also demonstrated in peripheral cells, such as endothelial cells and macrophages" (pg 846 of Kiemer et al. Endocrinology. 143: 846-852; reference CB on the 11/9/06 IDS). Furthermore, each of the references used in the instant rejection contain teachings consistent with this. Miyazawa et al and Suda et al each teach that "CNP occurs in a wide variety of tissues" (pg 3604 of Miyazawa et al; pg 2337 of Suda et al). Thus, at the time of filing of the instant application (3/31/05, with foreign priority claimed to 3/31/04), the person of ordinary skill in the art would not have understood CNP to be expressed exclusively in the brain, but rather would have understood CNP to be expressed in a wide variety of tissues.

The rejection set forth above is in accord with *International v. Teleflex Inc* (2007), as the embodiment rendered obvious by the combination of the references is not more than the predictable use of prior art elements according to their established function. The rejection does not speculate a "relationship" between CNP and GC-B. Instead, it cites the teachings of Suda et al that CNP is known to be a selective activator of GC-B. It further cites the informed speculation of Suda et al, based on the results of the experiments described in the paper, that "CNP is the endogenous ligand for GC-B in the bone in vivo and is involved in the process of endochondral ossification" (pg 2341). Furthermore, Miyazawa et al provide direct evidence that targeted expression of CNP in chondrocytes result in the same phenotype as BNP expressed systemically. The skilled artisan would have reasonably predicted that CNP exhibits similar effects *in vivo* and *in vitro* because Miyazawa shows that CNP transgenic mice exhibit elongated limbs in

accord with the phenotypes observed for BNP *in vivo* and CNP *in vitro*. Furthermore, the skilled artisan would have reasonably predicted that systemic CNP would result in the same phenotype as local administration based on the results with systemic administration of BNP, and the teachings of Suda et al suggesting that CNP is the actual ligand for GC-B in the bone rather than BNP. Furthermore, "an advantage" or "a motivation" is not a *per se* requirement for obviousness; in view of *KSR* a teaching-suggestion-motivation test for obviousness is but one possible approach; combining prior art elements according to known methods to yield predictable results is another, and which is applied in the rejection set forth herein.

New Claim Objections

Claims 1 and 22 are objected to because of the following informalities:

(1) In claim 1, lines 9-10, the recitation "by substituting the 32-53 amino acids thereof by any of the amino acid sequences of SEQ ID NOs: 3 to 10" should be written as "by substituting residues 32-53 of SEQ ID NO: 2 with any of the amino acid sequences of SEQ ID NOs: 3 to 10".

(2) Claim 22, lines 8-9, is objected to for the same reason as claim 1.

Appropriate correction is required.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Zachary C Howard/
Examiner, Art Unit 1646